Asymmetric hydrogenation of quinolines with high substrate/catalyst ratio

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The chiral diphosphinite ligand derived from (R)-1,1’-spirobiindane-7,7’-diol has been found to be highly effective in the Ir-catalyzed asymmetric hydrogenation of quinolines with high substrate/catalyst ratio (up to 5000) and high enantioselectivity (up to 94% ee).

Transition metal-catalyzed asymmetric hydrogenations have been extensively studied, and are considered as a versatile method for the preparation of optically active compounds.1,2 However, the enantioselective hydrogenation of heteroaromatic compounds, which is a convenient method for the preparation of enantiomerically pure heterocycles, still remains a challenging task. Successful examples in this type of asymmetric catalytic reactions are rare.3–6 Recently, Zhou and co-workers found that the iridium complex generated in situ from [Ir(COD)Cl]2 and (R)-MeO-BIPHEP or a ferrocenyloxazoline derived P,N-ligand was able to catalyse the enantioselective hydrogenation of quinolines with high enantioselectivities and good yields.5a,c Comparable results have also been achieved with the air-stable and recyclable Ir-P-Phos catalyst system.6a In a recent study, we found that the easily available, chiral phosphinite H8-BINAPO was an excellent ligand for the asymmetric hydrogenation of quinoline compounds with high enantioselectivities (up to 97% ee) and very good yields.6b Reetz and co-workers also demonstrated BINOL-derived diphosphonites with achiral P-ligands as additives to be highly efficient for the same reactions.7 On the other hand, Zhou et al. disclosed a new strategy for Ir-catalyzed asymmetric hydrogenation of quinolines by using chloroformate as activating reagent, and up to 90% ee was obtained.8d Although moderate to excellent enantioselectivities have been achieved, almost all these reactions suffered from low catalyst efficiency as evidenced by the fact that good results could only be obtained at a low substrate-to-catalyst ratio of 100. This might be due to the instability of the catalyst. From the viewpoints of both scientific interest and practical applications, it is highly desirable to develop more efficient catalysts for the highly enantioselective reaction.

In recent years, chiral ligands based on the 1,1’-spirobiindane backbone have been shown to be highly active and enantioselective in asymmetric hydrogenations, suggesting that the rigidity of the spirobiindane skeleton facilitated the effective transfer of chiral information.8 Following our pursuit of effective chiral phosphinite ligands for asymmetric hydrogenations,9a,b we herein report that an iridium catalyst containing a new chiral phosphinite ligand Spiropo (L1) (Scheme 1) derived from (R)-1,1’-spirobiindane-7,7’-diol exhibited high catalytic activity (substrate/catalyst ratio up to 5000 with 91% conversion) and excellent enantioselectivity (up to 94% ee) in the asymmetric hydrogenation of quinolines.

We first examined the performance of ligand L1 in the Ir-catalyzed hydrogenation of quinolines with 2-methylquinoline as a model substrate (Table 1). The catalyst was prepared in situ from L1 and [Ir(COD)Cl]2 with I2 as an additive. Under our previously optimized conditions,6b complete conversion and 92% ee were observed (entry 1). The catalyst was very stable in THF. Even after two months under an inert atmosphere, its activity and enantioselectivity still remained unchanged (entry 2). The reaction was sensitive to the solvents used (entries 3–6), and THF provided the best results. Similar solvent effect has been reported previously.6b By using THF as solvent, the effects of temperature and substrate-to-catalyst (S/C) molar ratio on the rate and enantioselectivity were examined. For comparison, the performance of (R)-H8-BINAPO (L2) (Scheme 1) was also investigated under otherwise identical conditions.

Slightly higher enantioselectivity was obtained with L1 when the reaction was carried out at 0 °C (entries 7–9). It was observed that the reaction proceeded smoothly at an S/C ratio from 100 to 2000 with complete conversions and high enantioselectivities using ligand L1 (entries 1, 7–9). When the S/C ratio was increased to 5000, the enantioselectivity still remained unchanged while the conversion decreased to 91% with L1 ligand (entry 10). It was noted that ligand L1 gave a high initial TOF value (2400 h−1 in the first hour) (entry 12). To the best of our knowledge, this is the best result reported so far for this reaction. In contrast,
Table 1 The catalytic activity of ligands L₁ and L₂ in the asymmetric hydrogenation of quinaldine

<table>
<thead>
<tr>
<th>Entry</th>
<th>L*</th>
<th>Solvent</th>
<th>S/C</th>
<th>Conv. (%)</th>
<th>Ee (%)</th>
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<tr>
<td>1</td>
<td>L₁</td>
<td>THF</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>L₁</td>
<td>THF</td>
<td>100</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>L₁</td>
<td>Toluene</td>
<td>100</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>L₁</td>
<td>Et₂O</td>
<td>100</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>L₁</td>
<td>CH₂Cl₂</td>
<td>100</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>L₁</td>
<td>CH₂OH</td>
<td>100</td>
<td>10</td>
<td>16</td>
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<tr>
<td>7</td>
<td>L₁</td>
<td>THF</td>
<td>500</td>
<td>100</td>
<td>92 (94)</td>
</tr>
<tr>
<td>8</td>
<td>L₁</td>
<td>THF</td>
<td>1000</td>
<td>100</td>
<td>92 (94)</td>
</tr>
<tr>
<td>9</td>
<td>L₁</td>
<td>THF</td>
<td>2000</td>
<td>100</td>
<td>92 (94)</td>
</tr>
<tr>
<td>10²</td>
<td>L₁</td>
<td>THF</td>
<td>2000</td>
<td>100</td>
<td>92 (94)</td>
</tr>
<tr>
<td>11</td>
<td>L₁</td>
<td>THF</td>
<td>5000</td>
<td>91</td>
<td>92 (92)</td>
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<tr>
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<td>L₁</td>
<td>THF</td>
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<td>76</td>
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<tr>
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<td>THF</td>
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<td>65</td>
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<tr>
<td>14</td>
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<td>L₁</td>
<td>THF</td>
<td>5000</td>
<td>7</td>
<td>67</td>
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</table>

*a* All reactions were carried out at room temperature with 0.15 mmol quinaldine (0.3 mmol for S/C 200/1 and 0.75 mmol for S/C 500/1) using Ir complex generated *in situ* from [Ir(COD)Cl]₂, ligand L₁ or L₂, and I₂ (1%) under 700 psi H₂ for 20 h (except for entries 10 and 12, 1 h) in 2 ml THF. *b* The catalyst was stored as a THF solution for two months before use. *c* The conversion was determined by 1H NMR and the enantioselectivity was determined by HPLC analysis with a Chiralpak OJ–H column. The product was in R-configuration. *d* The data in parentheses were obtained from reactions carried out at 0 °C.

Although ligand L₂ displayed somewhat better enantioselectivity at an S/C ratio of 100 (entry 13), both conversion and enantioselectivity dropped dramatically when the S/C ratio was increased from 500 to 5000 (entries 14–17). The effect of S/C ratio on catalysts with other bidentate phosphine ligands was also examined (Scheme 2). Considering the importance of solvent effect in this reaction, we employed the best solvent for each ligand employed: i.e. toluene for MeO-BIPHEP and BINAP, THF for P-Phos. With BINAP and MeO-BIPHEP, only 7 and 9% conversions at an S/C ratio of 2000 in 20 h were obtained, respectively, while with the P-Phos ligand, a complete conversion and 86% ee were observed under identical conditions. It was noted when the reaction time was reduced to 1 h, the (P-Phos)-Ir system provided the same enantioselectivity but substantially lower conversion (32%) compared to ligand L₁ (entry 10). In a similar manner, ferrocenylazoline ligand by Zhou⁵ only led to 67% conversion and 82% enantioselectivity in 12 h when the S/C ratio was 2000.

Table 2 Asymmetric hydrogenation of quinoline derivatives catalyzed by Ir–L₁ complex at high substrate/catalyst ratio in THF or DMPEG–hexane solvent systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sub.</th>
<th>Conv. (%)</th>
<th>Ee (%) in THF</th>
<th>Ee (%) in DMPEG–hexane</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>100 (100)</td>
<td>92 (92)</td>
<td>92</td>
</tr>
<tr>
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<td>100 (100)</td>
<td>87 (88)</td>
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<td>3</td>
<td>1c</td>
<td>100 (100)</td>
<td>90 (90)</td>
<td>91</td>
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<tr>
<td>4</td>
<td>1d</td>
<td>100 (100)</td>
<td>87 (87)</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>100</td>
<td>90</td>
<td>90</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>1g</td>
<td>66 (100)</td>
<td>92 (92)</td>
<td>92</td>
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<tr>
<td>8</td>
<td>1h</td>
<td>100</td>
<td>87</td>
<td>89</td>
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<tr>
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<tr>
<td>12</td>
<td>1l</td>
<td>100</td>
<td>92</td>
<td>92</td>
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</table>

*a* All reactions were carried out at room temperature with 0.15 mmol quinolines with an Ir complex generated *in situ* from [Ir(COD)Cl]₂, (0.05%) and ligand (0.1%), and I₂ (1%) under 700 psi H₂ for 20 h in 2 ml THF and/or MeO-PEG–hexane (1 : 1, v/v). *b* The conversions were determined by 1H NMR and the enantioselectivities were determined by HPLC analysis with a Chiralpak OJ–H (1a–1g), OD–H (1h and 1k), AS–H (1i and 1j) and OJ (1h) columns. The absolute configurations were assigned by comparison of the HPLC retention time with the reported data (all products were in R-configuration except for entries 8, 11 and 12). *c* Data were obtained at a substrate/catalyst ratio of 100.
was not observed in comparison with those obtained in THF solvent. The only exception was 2-phenylquinoline (II) (Table 2, entry 9), which gave 65% ee in DMPEG–hexane in comparison to the lower ee of 43% in THF.

The immobilization of chiral homogeneous catalysts have attracted much attention recently since it affords an attractive approach for the separation of product from the catalytic system and the recycling of the catalyst.11 Following our effort in this area,1a,12 we have recently found that the asymmetric hydrogenation of quinolines could be carried out smoothly in a DMPEG–hexane biphasic system, resulting in efficient separation and recycling of the catalyst.6a The recyclability of the complex Ir-L_4 in DMPEG–hexane was studied with the hydrogenation of 1a as a model reaction. At the end of each experiment the product was separated via simple decantation of the upper hexane layer followed by three additional extractions with degassed hexane. The results were summarized in Table 3. The conversion and enantioselectivity were consistent with the results obtained in THF.

In view of the high activity of the catalyst and the ready accessibility of the ligand, the method described here provides a practical route to optically active tetrahydroquinoline derivatives.

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Notes and references


